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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,409	01/23/2002	Maria Palasis	BSX:236US2	1618

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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

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01/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/057,409	PALASIS, MARIA	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-22,24,26-38,40-48 and 52-64* is/are pending in the application.

4a) Of the above claim(s) *16,18,20-22,26-37,41-48,52 and 53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,17,19,24,38,40,55-64* is/are rejected.

7)☒ Claim(s) *16,18,20-22,26-37,41-48,52 and 53* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/07 has been entered.

Claims 15, 17, 19, and 38 are amended.

Claims 4-11 and 54 are cancelled

Claims 63-64 are newly presented

Claims 4-11, 15-22, 24, 26-38, 40-48, and 52-64 are presently pending.

Election/Restrictions

In keeping with the prior restriction requirement, Claims 15, 17, 19, 24, 38, 40, and 54-62 are presently considered, with respect to the elected invention, and the balance of the presently pending Claims are withdrawn as being drawn to non-elected inventions.

Claim Status, Cancelled Claims

In light of Applicant's cancellation of Claims 4-11 and 54, all rejections and/or objections to such claims are withdrawn.

Claim Objections

Claims 16, 18, 20-22, 26-37, 41-48, and 52-53 are objected as being drawn to or encompassing non-elected inventions.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In light of the amendments, the rejections of Claims 17, 24, and 57-58 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods wherein the transgene is expressed by the BMS cells, does not reasonably provide enablement for the absence of expression, are withdrawn.

To wit, the claims have been amended to require expression of the transgene.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15, 17, 19, 24, 25, 38, 40, 54, 55, 57, 59, and 61 remain rejected, and Claims 63 and 64 are newly rejected, under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 7,097,832 to Kornowski, et al., Patented 8/29/06, and claiming priority to at least 8/5/00 and U.S.

Patent No. 7,186,688 and U.S. Patent No. 7,186,688 to Hu, et al, for reasons of record, reprinted below.

With regard to Claims 15, 17, 19, 38, 55, 57, 59, and 61, Kornowski teaches treatment of myocardial conditions with administration of autologous bone marrow (e.g., ABSTRACT), which may carry a transgene for an angiogenic growth factor, including HIF-1 (e.g., ABSTRACT; col. 2, paragraph 6). The bone marrow cells which may be transformed include the stromal cells (e.g., col. 16, paragraph 2). Further, the cells may be administered to tissue adjacent ischemic tissue (e.g., col. 15, paragraph 4). Such may be done to increase collateral blood vessel formation (e.g., col. 1, paragraph 2) and induce angiogenesis (e.g., col. 2, paragraph 3), and increase contractile function (e.g., EXAMPLE 4), in an ischemic heart myocardium (e.g., col. 2, paragraph 6). Moreover, the cells are modified to comprise the transgene *ex vivo* with e.g., a plasmid or adenoviral vector comprising the angiogenic transgene (e.g., col. 16, paragraph 2). Also, such HIF-1 production increases VEGF levels produced by the cells (e.g., col. 16, paragraph 2 and Claim 8), thereby modifying the cells to produce multiple angiogenic factors, including HIF-1 and VEGF. Still further, Kornowski teaches treatment of humans (EXAMPLE 6), with autologous cells (e.g., TITLE). Lastly, Kornowski teaches that such strategies can be simply to increase the production of VEGF and/or other cytokines with angiogenic activity (col. 16, paragraph 2).

With regard to Claims 24 and 40, the cells may be injected into multiple sites, including multiple sites adjacent to the ischemic zone (e.g., EXAMPLE 4).

With regard to Claim 54, the injection may be made by catheter (e.g., col. 10, paragraph 2).

With regard to Claims 63 and 64, electromechanical mapping is taught (e.g., EXAMPLE 6).

However, Kornowski does not specifically teach the use of a VEGF transgene, but only recognizes that such is successful to treat ischemic heart when administered transgenically via adenoviral vectors (e.g., cols. 1-2, paragraph bridging).

On the other hand, Hu teaches VEGF transgenes which can be used for angiogenic therapy in the myocardium (e.g., CLAIMS and col. 38, paragraph 5 and cols. 40-42).

Hence, at the time of invention, it would have been obvious to modify the methods of Kornowski with the VEGF transgene of Hu. The Artisan would have been motivated to do so as it was already known in the Art that VEGF transgenes could also produce beneficial effects to treat ischemic heart and Kornowski taught that other methods of increasing this factor's production would be successful and Hu demonstrates that the production of such protein can treat myocardium. Moreover, the Artisan would have had a reasonable expectation of success, as it was known in the art that VEGF was sufficient to produce increased angiogenesis.

Response to Argument – obvious, Kornowski and Hu

Applicant's argument of 10/31/07 has been fully considered but is not found persuasive.

Applicant argues that Kornowski teaches only a broad teaching of administration to an ischemic zone, and not adjacent tissue, and Hu does not teach or teach or suggest administration into normal myocardial tissue (pp. 10-11, paragraph bridging).

Such is not persuasive. Kornowski explicitly teaches administration to tissues adjacent the ischemic tissue, as was provided in the original rejection, and again as reprinted above (e.g., col. 15, paragraph 4 and EXAMPLE 4). (It is noted that EXAMPLE 4 teaches injections into an

ischemic zone, but the Artisan would read such to encompass delivery into the living tissue as well as the dead tissue.) Second, Hu does teach that VEGF can be expressed by way of a transgene, and further, that transgene delivery to cells which have undergone a procedure to model ischemic heart myocardial infarction may be treated to improve the heart's condition. Hence, the confluence of Kornowski and Hu demonstrate a clear motivation to so-administer VEGF.

Applicant argues that at the time of invention, Patterson, et al. (2999) Circulation, 99(20): 2614-16 argues against administration to tissue adjacent the diseased tissue, pointing to page 2614 (p. 11, paragraph 2).

Such is not persuasive. The cited reference specifically only states that two methods are currently being used to deliver the VEGF: arterial injections of VEGF protein into arteries supplying ischemic tissue; and delivery of plasmids encoding VEGF into ischemic zones. The reference in no way disparages the presently claimed invention, it just shows what Patterson believes are the general methods being followed, the two methods actually being a distinction between protein delivery and vector delivery, and the vagarities of "ischemic zones" leaves open the option of tissue adjacent the ischemic tissue. Hence, Patterson does not disparage the obvious methods.

Applicant argues that Mack, et al. (1998) Journal of Thoracic and Cardiovascular Surgery, 115(1): 168-77 argues against administration to tissue adjacent ischemic tissue in the heart (p. 11, paragraph 2).

Such is not persuasive. The reference states that they hypothesize the administration to regions of ischemic myocardium would enhance heart functions. However, such does not amount to being disparaging of the obvious methods.

Applicant argues that their findings are findings that evince unexpected results (pp. 11-13).

Such is not persuasive. It is wholly expected by the Artisan that injection into the region adjacent to the dead tissue would yield better results, as it is axiomatic that the dead tissue does not contribute to recovery. Hence, the VEGF, being expressed, would have a greater effect on the tissues when those tissues are living and not in the process of dying.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15, 17, 19, 24, 25, 38, 40, 54, 55, 57, 59, and 61 remain, and Claims 63 and 64 are newly, rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 7,097,832 to Kornowski, et al., Patented 8/29/06, and claiming priority to at least 8/5/00, and Safi, et al. (1999) Microvascular Resesearch, 58: 238-49.

With regard to Claims 15, 17, 19, 38, 55, 57, 59, 61, and 63-64, Kornowski teaches treatment of myocardial conditions with administration of autologous bone marrow (e.g., ABSTRACT), which may carry a transgene for an angiogenic growth factor, including HIF-1

(e.g., ABSTRACT; col. 2, paragraph 6). The bone marrow cells which may be transformed include the stromal cells (e.g., col. 16, paragraph 2). Further, the cells may be administered to tissue adjacent ischemic tissue (e.g., col. 15, paragraph 4). Such may be done to increase collateral blood vessel formation (e.g., col. 1, paragraph 2) and induce angiogenesis (e.g., col. 2, paragraph 3), and increase contractile function (e.g., EXAMPLE 4), in an ischemic heart myocardium (e.g., col. 2, paragraph 6). Moreover, the cells are modified to comprise the transgene *ex vivo* with e.g., a plasmid or adenoviral vector comprising the angiogenic transgene (e.g., col. 16, paragraph 2). Also, such HIF-1 production increases VEGF levels produced by the cells (e.g., col. 16, paragraph 2 and Claim 8), thereby modifying the cells to produce multiple angiogenic factors, including HIF-1 and VEGF. Still further, Kornowski teaches treatment of humans (EXAMPLE 6), with autologous cells (e.g., TITLE). Lastly, Kornowski teaches that such strategies can be simply to increase the production of VEGF and/or other cytokines with angiogenic activity (col. 16, paragraph 2).

With regard to Claims 24 and 40, the cells may be injected into multiple sites, including multiple sites adjacent to the ischemic zone (e.g., EXAMPLE 4).

With regard to Claim 54, the injection may be made by catheter (e.g., col. 10, paragraph 2).

With regard to Claims 63 and 64, electromechanical mapping is taught (e.g., EXAMPLE 6).

However, Kornowski does not specifically teach the use of a FGF-1 transgene, but only recognizes that such is successful to treat ischemic heart when administered transgenically via adenoviral vectors (e.g., col. 1, paragraph 3).

Moreover, at the time of invention, it had been shown in even more models that FGF, expressed transgenically in live tissue adjacent ischemic heart could increase angiogenesis and improve various parameters demonstrating improvements (e.g., Safi, et al. (1999) Microvascular Research, 58: 238-49, article in general, discussion in particular).

Hence, at the time of invention, it would have been obvious to modify the methods of Kornowski with the FGF-1 transgenes of Safi. The Artisan would have been motivated to do so as it was already known in the Art that FGF-1 transgenes could also produce beneficial effects to treat ischemic heart. Moreover, the Artisan would have had a reasonable expectation of success, as many models had demonstrated increased angiogenesis.

Response to Argument – Obviousness, Kornowski and Saffi

Applicant's argument of 10/31/07 has been fully considered but is not found persuasive.

Applicant argues that Kornowski does not teach FGF, that Kornowski only teaches administration to an ischemic zone rather than border area of the infarct (p. 13, paragraph 3).

Such is not persuasive. Kornowski does teach the border of the infarct, as again shown above. The Examiner requests Applicant to reread the rejection, resupplied above.

Applicant argues that Safi does not teach treating ischemic tissue, but is limited to healthy heart tissue (p. 13, paragraph 3).

Such is not persuasive. Safi also shows that recombinant angiogenic proteins work in the presence of chronic ischemic, including when performed by vector administrations (p. 245, col. 1, paragraph 2). It is difficult for the Examiner to say that this would preclude working in the presently claimed invention.

Applicant argues that the references do not teach or suggest the use of the recited delivery devices of Claims 15, 17, 19, or 38.

Such is not persuasive. At least Example 6 teaches a needle catheter. Moreover, the delivery methods are standard in the Art for delivery of materials to the heart, and hence, they are instantly obvious to the Artisan as the Artisan needs a method to deliver such substances.

Applicant argues unexpected results (pp. 13-14, paragraph bridging).

Such is not persuasive. As discussed above, it is a case of simple logic that the response would be better.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15, 17, 19, 38, 24, 54, 56, 58, 60, and 62 remain, and Claims 63-64 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 7,097,832 to Kornowski, et al., Patented 8/29/06 and U.S. Patent No. 7,186,688 to Hu, et al., as applied to claims 15, 17, 19, 24, 25, 38, 40, 54, 55, 57, 59, and 61 above, and further in view of U.S. Patent No. 5,800,539 to Waller; and

Claims 15, 17, 19, 38, 24, 54, 56, 58, 60, and 62 remain, and Claims 63-64 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 7,097,832 to

Kornowski, et al., Patented 8/29/06, and claiming priority to at least 8/5/00, and Safi, et al. (1999) Microvascular Resesearch, 58: 238-49, as applied to claims 15, 17, 19, 24, 25, 38, 40, 54, 55, 57, 59, and 61 above, and further in view of U.S. Patent No. 5,800,539 to Waller.

As shown above, Kornowski and Hu or Kornowski and Saffi each make obvious the various aspects of the invention, except that of the use of allogenic BMS cells.

However, Waller teaches the use of allogenic BMS cells for transplantation (e.g., ABSTRACT; CLAIMS). Moreover, such can be performed without lethal graft versus host disease (ABSTRACT).

Hence, at the time of invention it would have been obvious to modify Kornowski or Kornowski/Saffi with the allogenic BMS of Waller. The Artisan would have been motivated to do so because Waller teaches that such may be performed with causing lethal graft versus host disease. Moreover, the Artisan would have had a reasonable expectation of success, as Kornowski and Kornowski/Saffi had demonstrated that the transplant would be efficacious and Waller teaches that allogenic cells could be used in transplants.

Response to Argument – Obviousness, Kornowski, Hu, and Waller

Applicant's argument of 10/31/07 has been fully considered but is not found persuasive.

Applicant rehashes the arguments the base claim rejections, above (p. 14).

Such is not persuasive. Applicant is directed to the answers provided above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15, 17, 19, 24, 38, 40, 55-64 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over either (i) Kornowski and Hu; (ii) Kornowski and Saffi; (iii) Kornowski, Hu, and Waller; or (iv) Kornowski, Saffi, and Waller, as applied to Claims: (i) 15, 17, 19, 24, 25, 38, 40, 54, 55, 57, 59, 61, and 63-64; (ii) 15, 17, 19, 24, 25, 38, 40, 54, 55, 57, 59, 61, and 63-64; (iii) 15, 17, 19, 38, 24, 54, 56, 58, 60, 62, and 63-64; or (iv) 15, 17, 19, 38, 24, 54, 56, 58, 60, and 62-64, respectively, above, and further in view of U.S. Patent Publication No. 2002/0061587 to Anversa, claiming priority to July 31, 2000.

As shown above, the various rejections make obvious to the Artisan the presently claimed inventions. However, the single important aspect that the Examiner hopes to address here is that administration to the region adjacent the ischemic tissue is obvious. Anversa is used for such.

Anversa teaches improving ventricular function of an infracted myocardium by administration of bone marrow stem cells, in combination with a cytokine such as VEGF, G-CSF, GM-CSF, SCF, and others, or any cytokine capable of stimulating or mobilizing the stem cells (paragraph 44). The cytokine may be via a vector that expresses the cytokine, and the vector may be a cell modified ex vivo (paragraph 130). Also, Anversa discloses administrations to the border of the infarct area, which cannot be denied is delivery adjacent (paragraph 140 and EXAMPLES).

Hence, the methods are even more obvious. The Artisan would have performed the methods to treat the various heart conditions for improving function. Moreover, the Artisan would have expected success, as Anversa teaches such.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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